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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,162	05/05/2006	Fabrizio Gasparini	33364-US-PCT	6619
67283 7590 01/05/2009 MONTGOMERY, MCCrackEN, WALKER & RHOADS, LLP 123 SOUTH BROAD STREET AVENUE OF THE ARTS PHILADELPHIA, PA 19109				
EXAMINER ROBINSON, BINTA M				
ART UNIT		PAPER NUMBER		
1625				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/573,162

Applicant(s)

GASPARINI ET AL.

Examiner

BINTA M. ROBINSON

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SF 298)
Paper No(s)/Mail Date 3/23/2006
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date ____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: ____

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1, 2, 4, 5 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 5, 6 of copending Application No. 11823310 (See US PG Pub 2007/02652279 A1) in view of Patani et. al. Although the conflicting claims are not identical, they are not patentably distinct from each other because a genus of compounds and compositions containing them which overlap in subject matter with the instant genus of compounds and compositions differing structurally only in the trivalent substitution in the 4 position within the pyridine ring of the compound. The copending compounds have antagonistic activity at the mGluR5 receptors, while the instant compounds are useful as markers for labeling the central and peripheral mGlu5 receptors.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The copending application teaches a genus of compounds and compositions



used as mGlu R5 antagonists of formula II, wherein A is $\text{=N-O-(C}_{1-4}\text{)alkyl}$, R is methyl, and R_{IV} and R_V are hydrogen. See the genus of compounds of formula II at page 11 and compositions at claim 5-6. The difference between the copending compounds and compositions and the instantly claimed compounds and compositions is the teaching of a generic compound wherein at the 4 position of the pyridyl ring, there is a -C= in the instant genus of compounds, versus a -N= at the 4 position, such that the ring is a piperazinyl ring rather than a pyridyl ring in the copending compounds and compositions. The other difference is that the copending compounds and compositions are used as mGluR5 antagonists rather than as markers for labeling the central and peripheral mGlu5 receptors. Patani et. al., teaches that a classical bioisosteric replacement is -C= with -N= . See Part C of page 3156 of Patani et. al. Bioisosteres are compounds which retain similar pharmacological activities and elicit similar biological activities due to similar physiochemical properties. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds and compositions containing them which are bioisosteres of one another and which have activity with regards to the mGlu5 receptor. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for

the claimed compounds and compositions over those of the generic copending compounds and compositions.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 2, 4, 5 are provisionally rejected under 35 U.S.C. 103(a) as being obvious over copending Application No. 11823310 (See US PG Pub 2007/02652279 A1) in view of Patani et. al. which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if published or patented. This provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future publication or patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application prior to the effective U.S. filing date of the copending application under 37 CFR 1.131. This rejection might also be overcome by showing that the copending application is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(I)(1) and § 706.02(I)(2).

The copending application teaches a genus of compounds and compositions used as



mGlu R5 antagonists of formula II, wherein A is

, R_{II} and R_{III} come together to form =N-O-(C₁₋₄)alkyl, R is methyl, and R_{IV} and R_V are hydrogen. See the genus of compounds of formula II at page 11 and compositions at claim 5-6. The difference between the copending compounds and compositions and the instantly claimed compounds and compositions is the teaching of a generic compound wherein at the 4 position of the pyridyl ring, there is a -C= in the instant genus of compounds, versus a -N= at the 4 position, such that the ring is a piperaziny ring rather than a pyridyl ring in the copending compounds and compositions. The other difference is that the copending compounds and compositions are used as mGluR5 antagonists rather than as markers for labeling the central and peripheral mGlu5 receptors. Patani et. al., teaches that a classical bioisosteric replacement is -C= with -N=. See Part C of page 3156 of Patani et. al. Bioisosteres are compounds which retain similar pharmacological activities and elicit similar biological activities due to similar physiochemical properties. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds and compositions containing them which are bioisosteres of one another and which have activity with regards to the mGlu5 receptor. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds and compositions over those of the generic copending compounds and compositions.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of formula I that are 3-(6-methyl-pyridine-2-ylethynyl)-cyclohex-2-enone O-[C-methyl]-oxime does not reasonably provide enablement for using any other compounds of formula I as claimed. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized below. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art 6) the amount of direction provided by the inventor 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In *re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

a) Determining if any particular claimed compounds of formula I other than 3-(6-methyl-pyridine-2-ylethynyl)-cyclohex-2-enone O-[C-methyl]-oxime would be

active would require synthesis of the substrate and subjecting it to testing with Applicants' binding assay and brain distribution study. Considering the number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found at pages 4 through 7. c) In the instant case, none of the working examples involves the use of claimed compounds other than 3-(6-methyl-pyridine-2-ylethynyl)-cyclohex-2-enone O-[C-methyl]-oxime in the binding assay or in the brain study.

d) The nature of the invention is using the compounds to label brain and peripheral nervous system structures involving mGlu5 receptors with Applicants' compounds. The nature of the invention requires an understanding of the mGlu5 receptor, the binding activity of small ligands to that receptor, and the ability of those compounds to label brain and peripheral nervous system structures. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied characteristics the skilled artisan would indeed question the inclusion of such compounds claimed, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) There is no reasonable basis for the assumption that the myriad of compounds embraced by the present formula (I) will all share the same biological

and chemical properties. For example, compounds of formula I with R equal to CH₃ would not be obvious over compounds with R equal to CH₂Br, wherein n is 3 or 4. Many of the diverse claimed compounds are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology and medicinal chemistry that structurally dissimilar compounds will have the same or similar activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouche*, 169 USPQ 429 at 434 (a Markush group including both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part

to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

f) The artisan using Applicants' invention to label the brain with the claimed compounds would be a physician with a MD degree or a pharmacologist or medicinal chemist with a PhD and several years of experience. He would be unaware of how to predict *a priori* how a changing one nonobvious moiety to another would affect biological and chemical activity. In view of the divergent moieties claimed with varied biological and chemical properties, the skilled artisan would indeed question the inclusion of such diverse compounds, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all compounds of formula (I). The present claims embrace various radicals, which are not art-recognized as equivalent. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 6 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 6 is indefinite, because there is no reference to what host the labelling is taking place in.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Janet Andres can be reached on 571-272-0670.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

/Binta M Robinson/
Examiner, Art Unit 1625

/Janet L. Andres/
Supervisory Patent Examiner, Art Unit 1625